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EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
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13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/043,833	Applicant(s) WELLS ET AL.	
	Examiner Jon D Epperson	Art Unit 1639	

-- Th MAILING DATE of this communication appears on the cover she t with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 May 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40,41,44-53,56 and 63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,41,44-53,56 and 63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). *13* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the Application

1. The Response filed May 19, 2003 (Paper No. 12) is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

3. Claims 40-62 were pending (see Paper No. 11). Applicants cancelled claims 42-43, 54-55 and 57-62; added claim 63 and amended claims 50, 50 and 52 (see Paper No. 12, page 4, paragraph 1). Therefore, claims 40-41, 44-53, 56 and 63 are currently pending.

Withdrawn Objections/Rejections

4. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC § 112, first paragraph

5. Claims 40-41, 44-53, 56 and 63 are rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 USC 112, ¶ 1 "Written

Description" Requirement, Federal Register, Vol. 66, No. 4 pages 1099-1111, Friday January 5, 2001. This is a written description rejection.

These claims encompass a broad genus. For example, claim 40 outlines method steps for screening a library of "small organic compounds" using a "target protein-ligand conjugate" with "first" and "second" reactive functionalities, wherein no structural features or identifying characteristics are given for the "small organic molecules", "target protein-ligand conjugate" or the "first" and "second" reactive functionalities. The scope of this claim includes an infinite number of methods for identifying an infinite number of small organic compounds using an infinite number of target proteins and an infinite number of ligands. Furthermore, the specification and claims do not place any limit on the number of atoms, the types of atoms, or the manner in which said atoms might be connected to form the "target protein", "ligand", "small organic compounds", or the "first" and "second" reactive functionalities contained therein. Consequently, it is not possible to determine *a priori* which "proteins", "ligands", "small organic molecules", "first and second functionalities" would be encompassed by the present claims because there is no commonality that can link together ***all*** of these unknown variables i.e., there is no teaching that would allow a person of skill in the art to determine *a priori* what "proteins", "ligands", "small organic molecules" and "functionalities" should be included in this genus from the lack of working examples provided by applicants (i.e., Applicants provide NO working examples of an "extended" tethering screening technique). Furthermore, a person of skill in the art would not know what "small organic molecules" to screen even if Applicants disclosed what "proteins" and "ligands" that were being used (i.e., Applicants provide no starting point for the screening).

The general knowledge and level of skill in the art do not supplement the omitted description because specific, ***not general***, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is enormous and highly variant, simply reciting a "laundry list" of potential biological target molecules, chemically reactive groups and target proteins (e.g., see specification, page 8, last paragraph, wherein target protein may be "enzymes, such as proteases and thymidylate synthease, steroid receptors, nuclear proteins, allosteric enzyme inhibitors, clotting factors ... etc.") is insufficient to teach the entire genus. Consequently, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe this enormous genus. Thus, applicants were not in possession of the claimed genus.

Response

6. Applicant's arguments directed to the above Written Description rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues that **[1]** the present invention is not directed to target proteins or ligands (i.e., the target protein(s) and ligand(s) are "not critical" to the invention) but rather concerns "broadly applicable screening methods" and, as a result, Applicants do not have to describe these non-essential features. Applicants further state that the "operability" of the invention is not

limited to any particular protein, ligand, small organic molecule, or linking group structure. Applicants further point out that they do provide a "single" working example of a cysteamine-modified thymydilate synthase in conjunction with some aldehyde ligands (see Paper No. 12, page 6, last two paragraphs to page 7, paragraphs 1-2; see also page 8, last paragraph), **[2]** "[t]he Examiner has given no reason why one skilled in the art would not reasonably accept that the screening method of the invention can be performed with any target protein and any ligand, capable of forming any type of covalent bond, i.e., that applicants were in possession of the invention" (see Paper No. 12, page 8., paragraph 1), **[3]** The Examiner's statement that the claims include an "infinite number of methods" is clearly in error ... the claims are directed to a particular, well defined method" (see Paper No. 12, page 8, paragraph 3), **[4]** "Applicants are at a loss to understand the Examiner's reference to the extensive teaching in the specification as a "laundry list" of potential biological target molecules, chemically reactive groups and target proteins. It is hard to imagine how else Applicants could provide guidance in the specification buy by providing an extensive listing of exemplary embodiments" (see Paper No. 13, page 9, paragraphs 1-3, especially paragraph 3).

This is not found persuasive for the following reasons:

The Examiner contends that **[1,3]** that the target protein(s), ligand(s) and linker(s) are critical to the invention because the claimed "tethering" method could not be performed without them. It means little to "invent" a method if one does not have possession of all the essential ingredients that are required to practice said method. If Applicants do not have possession of all the claimed target protein(s), ligand(s) and linker(s) then Applicants do not have possession of all the methods for using said protein(s), ligand(s) and linker(s) (i.e., Applicants are not claiming

"one" method but an "infinite" number of methods using an "infinite" number of proteins, ligands, etc). Without all of the claimed protein(s), ligand(s) and linker(s), the claimed invention is more theoretical than real. Here, Applicants have admitted that their claimed scope is broad (see Paper No. 12, page 6, paragraph 3, "broadly applicable screening method") and could employ *any* protein, ligand and linker (i.e., Applicants claims encompass an infinite number of possibilities). Therefore, Applicants must provide an adequate written description for these claimed "essential" materials (i.e., the infinite number of possibilities) and their method of use within the "full scope" of the claimed invention.

The Examiner further contends that Applicants must set forth a "representative number of examples" that would allow a person of skill in the art to determine that Applicants had possession of the full scope of the claimed invention (i.e., adequate written description). With respect to adequate disclosure of the scope of the presently claimed generic Applicants are referred to the discussion in *University of California v. Eli Lilly and Co.* (U.S. Court of Appeals Federal Circuit (CAFC) 43 USPQ2d 1398 7/22/1997 Decided July 22, 1997; No. 96-1175) regarding disclosure. For adequate disclosure, like enablement, requires *representative examples* that provide reasonable assurance to one skilled in the art that the compounds falling within the scope both possess the alleged utility and additionally demonstrate that *applicant had possession of the full scope of the claimed invention*. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724 (for enablement) and University *of California v. Eli Lilly and Co* cited above (for disclosure). The more unpredictable the art the greater the showing required (e.g. by "representative examples") for both enablement and adequate disclosure. Here, Applicants have not provided ***any*** working

examples. The Example, Applicants allude to i.e., the cysteamine-modified thymydilae synthase and aldehyde ligands (see Paper No. 12, page 7, paragraph 3) would not fall within the scope of claim 40 because it does not represent an "extended" tethering method. In Applicants' example the "protein" is the "cysteamine-modified thymydilate synthase", the "ligands" are the "aldehydes", but Applicants provide "NO EXAMPLES" of the "small organic molecules" that would react with these protein-ligand conjugates. The only "evidence" that is used to support the currently claimed invention is Applicants' unsubstantiated statement that "one of skill in the art would appreciate that the same type of chemical reaction could be used, for example, to build off of the ligand covalently bound to the cysteamine-modified thymydilate synthase" (see Page 7, paragraph 3). The Examiner contends that this is a glaring omission of essential information that would be required to adequately describe Applicants' claimed invention. In addition, even if *assuming arguendo* that a person of skill in the art would consider this "working" example to be adequate, the Examiner contends that "one" example is not sufficient to teach an infinite number of possibilities that are currently claimed.

In addition, as stated in the original rejection, the general knowledge and level of skill in the art do not supplement the omitted description because specific, ***not general***, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify ***all*** of the members of the genus or even a substantial portion thereof, and because the genus is ***enormous*** and ***highly variant***, simply reciting a "laundry list" of potential ligands, chemically reactive groups and target proteins (e.g., see specification, page 8, last paragraph, wherein target protein may be "enzymes, such as proteases and thymidylate synthease, steroid receptors, nuclear proteins, allosteric enzyme inhibitors, clotting factors ... etc.") is insufficient to

teach the entire genus. Furthermore, the Examiner contends that the art is inherently unpredictable because the genus is enormous and highly variant and thus would require even a greater number of examples than an invention narrowly constrained to predictable class of compounds.

The Examiner contends **[2]** that Applicants have not provided a "representative" number of Examples that would allow a person of skill in the art to determine that they were in possession of the claimed invention (see above). Furthermore, the Examiner contends that the Art is inherently unpredictable (see below) and would require an even greater showing of "representative" examples than a more predictable art area.

Applicants requested that the Examiner "provide specific scientific reasoning why one skilled in the art would not accept that at the effective filing date of the present application applicants were in the possession of the invention" (see Paper No. 10, page 9). As requested, the Examiner sets forth a new reference (see Delano, W. L. "Unraveling hot spots in binding interfaces: progress and challenges" *Current Opinion in Structural Biology* **2002**, *12*, 14-20) for the sole purpose of adhering to Applicants' request. However, please note that the Examiner does not believe that such a reference is necessary because as stated above (and also in the original rejection) Applicants disclosure of only "one working example" is not "representative" of such broad scope.

Delano (see entire document) outlines some of the challenges faced by today's researchers that are trying to analyze "hot spots" in protein-binding interfaces (e.g., proteins that bind to other proteins and/or other ligands). The reference explicitly cites Applicants claimed invention (see Reference 47-48 therein) and thus is a particularly relevant reference (i.e., the

reference represents analogous art). Delano states that "there are no general patterns of hydrophobicity, shape or charge that can be used as a basis for predicting which protein atoms will participate in hot spots" (see Delano, page 14, column 1, paragraph 2) and defines said hot spots as "a residue that, when mutated to alanine, gives rise to a distinct drop in the binding constant (typically tenfold or higher) [of a protein and/or another ligand]" (see Delano, page 14, column 2, paragraph 2; please note that this technique is called "alanine scanning"). Delano goes on to further define potential destabilizing perturbations that occur as a result of these "alanine mutations" in protein-ligand interactions as "(a) loss of optimal van der Waals contacts; (b) loss of electrostatic pairings ... and (i) global unfolding" (see Delano, page 16, figure 3).

Here, the Examiner contends that Applicants claimed method requires "mutations" in the target protein (i.e., to equip the protein with a chemically active group at or near a site of interest which facilitates covalent bonding to the ligand) that would prevent said target protein from binding to its ligand(s) and/or small organic compounds just as the "alanine mutations" interfered with the protein-protein and/or protein-ligand interactions in Delano via "(a) loss of optimal van der Waals contacts; (b) loss of electrostatic pairings ... and (i) global unfolding" (see Delano, page 16, figure 3). Consequently, the Examiner contends that Applicants are not in possession of the full scope of the claimed invention because Delano states that "there are no general patterns of hydrophobicity, shape or charge that can be used as a basis for predicting which protein atoms will participate in hot spots [i.e., which protein atoms when mutated will destabilized the protein and/or prevent ligand binding]" (see Delano, page 14, column 1, paragraph 2) and, as a result, Applicants would not be able to determine *a priori* whether their required "mutations" would or would not destabilize, unfold and/or prevent their target proteins

from covalently bonding to their respective ligands at a site of interest. Just because Applicants have shown that a thymydilate synthase can be "mutated" with a cysteamine and still retain its ability to bind to a ligand does not mean that all proteins, ligands and linkers will act in a similar manner. Furthermore, given the specificity and fragile nature of protein-ligand interactions and the myriad of mechanisms by which a simple seeming innocuous mutation can unpredictably destabilize and/or prevent ligand binding, the Examiner contends that the majority of Applicants claimed embodiments would be inoperative (see Delano, figure 3 which outlines just how unpredictable the effects of protein mutations can be, "In particular, changes in interface dynamics are very hard to demonstrate or rule out experimentally because of the limitations of available technology. These effects, which relate to the plasticity of protein interfaces, account for much of the current uncertainty in the interpretation of alanine scanning data [i.e., what happens to the stability of a protein when it is mutated as is the case here]").

Finally, the Examiner contends **[4]** that Applicants claimed invention is essentially drawn to a "trial and error" method for discovering a "small organic compound" that binds covalently to a "protein-ligand conjugate." The specification, however, does not provide any guidance in the way of selecting a particular "small organic compound" for screening (i.e., Applicants single "working" example does not disclose the identity of any "small organic compounds", see Paper No. 12, page 7, paragraph 3). Furthermore, the specification does not provide any means for narrowing this infinite number of possible candidate "small organic compounds" to a more manageable list because the specification only discloses one "working" example with particularity (i.e., the other cysteamine-modified thymydilate synthase).

Consequently, although the present application describes an assay for determining whether a given "small organic molecule" possesses certain desired functional characteristics (i.e., the ability to covalently bind to a protein-ligand conjugate), and identifies some broad categories of compounds that *might* function as the small organic molecules, proteins and ligands (i.e., the "laundry list"), these descriptions, without more precise guidelines, amount to little more than "a starting point, a direction for further research." *Genentech*, 108 F.3d at 1366. *See also Calgene*, 188 F.3d at 1374 ("the teachings set forth in the specifications provide no more than a 'plan' or 'invitation' for those of skill in the art to experiment practicing [the claimed invention]; they do not provide sufficient guidance or specificity as to how to execute that plan") (emphasis added). The courts have repeatedly stated, "A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion" (See *Brenner v. Manson*, 383 U.S. 519, 536 (1966)). Here, Applicants only "working" example fails to show essential claimed subject matter with particularity (i.e., the small organic compounds). Consequently, the Examiner contends that Applicants disclosure represents a mere "wish" or "plan" for further research.

Accordingly, the Written Description rejection cited above is hereby maintained.

Claims Rejections - 35 U.S.C. 102

7. Claims 40-41, 44-46 are rejected under 35 U.S.C. 102(b) as being anticipated by Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**).

For **claim 40**, Pitner et al (see entire document) teaches a method for modifying antibodies, which anticipates claim 40. For example, Pitner et al discloses [a] screening a library of small organic compounds e.g., antibody antigens (see Pitner et al, figure 1; see also figure 6 showing PC and PC-TP antigens; see also Figure 7 showing PC and PC-MAL antigens; see also Figure 11 showing GlcNAc and GlcNAc-TP antigens; see also Figure 12 showing GlcNAc and ClcNAc-MAL antigens), [b] with a target protein ligand conjugate formed by the covalent bonding of a biological target molecule comprising a first reactive functionality with a compound that comprises (1) a second reactive functionality and (2) a chemically reactive group, wherein the second reactive functionality of the compound reacts with the first reactive functionality of the biological target molecule to form a first covalent bond such that the protein-ligand conjugate contains a free chemically reactive group (see Pitner et al, figure 1 wherein said target biological molecule is the McPC603 antibody, the first reactive functionality is the -NH2 group on the antibody, the second reactive functionality is the ketone on the affinity label that reacts with the -NH2 group to form a covalent bond, the chemically reactive group is the -S-S- that is set "free" in DTT to become an –SH) (i.e., the newly modified antibody with the free –SH is the "protein-ligand conjugate") (emphasis added), [c] wherein at least one member of the library forms a second covalent with the target protein-ligand conjugate (see Pitner et al, figure 5 wherein the target-protein ligand conjugate is McPC603-SH and the "at least one member of the library" is PC-TP; see also figure 6 wherein the "at least one member of the library" is PC-MAL; see also figures 11 and 12, using modified st9 and GlcNAc antigens), [d] identifying a small organic compound that

binds covalently to the chemically reactive group thereby forming a complex (see figures 5-6 and 11-12 showing antigen/antibody binding curved e.g., "identification" of which antigens bind and by how much).

For **claim 41**, Pitner et al discloses the second covalent bond is a disulfide bond (see Pitner et al, figure 1, see also column 6, paragraph 2).

For **claim 44**, Pitner et al discloses a free thiol (see Pitner et al, figure 1, see also column 6, paragraph 2).

For **claim 45**, Pitner et al discloses library members with thiols and disulfides (see Pitner et al, figure 1, see also column 6, paragraph 2).

For **claim 46**, Pitner et al discloses all library members with amides (see Pitner et al, figure-8 showing all GlcNAc library members with NHAc groups).

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues **[1]** that the "antibody-antigen conjugate" does not contain a "free chemically reactive group" on the "ligand" as required by Applicants' newly amended claims. (see Paper No. 12, page 10) and **[2]** Pitner et al does not describe the identification of a small

organic compound that binds covalently to the chemically reactive group of the protein ligand conjugate.

This is not found persuasive for the following reasons:

The Examiner contends **[1]** that it is not clear what "ligand" Applicants are referring to in newly amended claim 40 (see 35 U.S.C. § 112, second paragraph rejection below) and, as a result, Pitner et al is still applicable. In Pitner et al, a "target protein" (i.e., the antibody) is reacting with a "modifying group" (i.e., the affinity label) to form a "modified target protein" (i.e., the antibody modified to contain a free thiol). The Examiner contends that said "modified target protein" (i.e., the antibody with the free thiol) falls within the scope of Applicants' claimed "protein-ligand conjugate." The Examiner is not contending (as purported by Applicants, see Paper No. 12, page 10) that the "protein-ligand conjugate" is the "antibody-antigen" complex (the Examiner agrees that this antibody-antigen complex does not have Applicants' claimed free reactive group). Rather, the Examiner contends that the "protein-ligand conjugate" is the "modified target protein itself" without the antigen. The Examiner contends that this position is reasonable in light of Applicants indefinite claim language (see 35 U.S.C. § 112, second paragraph rejection below), which does NOT state that a "ligand" binds to the protein to form a protein-"ligand" conjugate. Rather, claim 40 only states that a "***compound***" (not a ***ligand***) binds to the protein (emphasis added), which implies that the "target protein itself" should be regarded as the "ligand" (i.e., a ligand for the "small organic compounds"). Why else would Applicants make the distinction between the "compound" and the "ligand" if not to show that the "compound" could be something other than a ligand (Please note that the use of more than one term to refer to the same chemical entity, if that is what is going on here, is confusing, see 35

U.S.C. 112, second paragraph rejection below). The "protein ligand" would also still be considered a "conjugate" in this scenario because it is conjugated to the "modifying group." To summarize, the "protein-ligand conjugate" in Pitner et al is the "-SH modified antibody" that does contain a "free chemically reactive" (i.e., an "-SH group") for covalent bonding to "small organic molecule" (i.e., "antigens") as outlined in the original rejection above.

Furthrmore, the Examiner contends **[2]** that Pitner et al does describe the identification of a small organic compound covalently bound to the protein-ligand conjugate. As discussed above the "protein-ligand conjugate" is the –SH modified antibody which does bind covalently to a variety of small organic molecules i.e., the various "antigens" represent the "small organic molecules" (see Pitner et al, figure 1; see also figure 6 showing PC and PC-TP antigens; see also Figure 7 showing PC and PC-MAL antigens; see also Figure 11 showing GlcNAc and GlcNAc-TP antigens; see also Figure 12 showing GlcNAc and ClcNAc-MAL antigens).

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

9. Claims 40-41, 44-46 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Janda et al (Janda, K. D.; Lo, C. –H. L.; Li, T.; Barbas, C. F.; Wirsching, P.; Lerner, R. A. "Direct selection for a catalytic mechanism from combinatorial antibody libraries" *PNAS* **March 1994**, *91*, 2532-2536).

For **claim 40**, Janda et al (see entire document) teaches a method for screening a combinatorial antibody library for enzymatic activity, which anticipates claim 40. For example, Janda et al discloses [a] screening a library of small organic compounds e.g.,

catalytic antibody substrates (see Janda et al, figure 1, compounds 1-6, see also page 2533, column 1, paragraph 2 for generation of antibody library), [b] with a target protein ligand conjugate formed by the covalent bonding of a biological target molecule comprising a first reactive functionality with a compound that comprises (1) a second reactive functionality and (2) a chemically reactive group, wherein the second reactive functionality of the compound reacts with the first reactive functionality of the biological target molecule to form a first covalent bond such that the protein-ligand conjugate contains a free chemically reactive group (see Janda et al, figures 1-2 showing reaction of compound 1 with BSA wherein compound 1 is a "compound" that contains "a second reactive functionality" (i.e. the N-hydroxysuccinimide ester) that reacts with a "first reactive functionality" on the target protein (i.e. an amino group) to form a covalent bond leaving a disulfide bond or a free –SH under exchanging condition (i.e., a free chemically reactive group) for covalent attachment to the antibody [c] wherein at least one member of the library forms a second covalent with the target protein-ligand conjugate (see Janda et al, figure 2; see also page 2533, column 2, last two paragraphs), [d] identifying a small organic compound that binds covalently to the chemically reactive group thereby forming a complex (see Janda et al, page 2533, last paragraph; see also Materials and Methods section).

For **claim 41**, Janda et al discloses the second covalent bond is a disulfide bond or a free –SH group under exchange conditions (see Janda et al, figure 2 showing formation of disulfide).

For **claim 44**, Janda et al discloses a free thiol (see Janda et al, figure 2).

For **claim 45**, Janda et al discloses library members with thiols and disulfides (see Janda et al, figures 1-2).

For **claim 46**, Janda et al discloses all library members with amides (see Janda et al, figure 2).

For **claim 56**, Janda et al discloses enzymes i.e., catalytic antibodies (see Janda et al, abstract).

Response

10. Applicant's arguments directed to the above 35 U.S.C. § 102 rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues **[1]** that "one fallacy ... is that the compound of formula 1 is not considered a ligand by the definition of the present invention" and, as a result, Janda et al does not disclose all elements of the process claimed (see Paper No. 12, pages 11-12) and **[2]** the disulfide bond in Janda et al is not a "free chemically reactive group" within the terminology of claim 40 (see paper No. 12, page 12, last paragraph to page 13).

This is not found persuasive for the following reasons:

The Examiner contends **[1]** that compound of formula 1 does not have to be a "ligand" as alluded to above. Claim 40 only states that a "compound" (not a "ligand") (emphasis added) binds to the target protein and "compound 1" clearly falls within the definition of a "compound"

(please also see similar analysis above for Pitner et al rejection under 35 U.S.C. § 120). Furthermore, the "compound 1" is a "ligand" because it does not need to have an "affinity for a particular site." In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "affinity for a particular site") are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Furthermore, the Examiner contends **[2]** that Janda et al discloses a free –SH in addition to a disulfide group as outlined in the original rejection (e.g., see Janda et al, figure 2), which meets Applicants claims.

Accordingly, the 35 U.S.C. 102 rejection cited above is hereby maintained.

Claim Rejections - 35 USC § 103

11. Claims 40-41, 44-49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is November 22, 1994) and Loo, J. A. (Loo, J. A. "Studying Noncovalent Protein Complexes by Electrospray Ionization Mass Spectrometry" *Mass Spectrometry Reviews*, **1997**, *16*, 1-23).

For **claims 40-41 and 44-46**, Pitner et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which

anticipates claims 40-41 and 44-46 and, consequently, also renders obvious claims 40-41 and 44-46.

The prior art teachings of Pitner et al differ from the claimed invention as follows:

For **claims 47-48**, Pitner et al is deficient in that it does not specifically teach the use of "mass spectrometry" for the identifying step. Pitner et al used UV/Vis for detection.

For **claim 49**, Pitner et al is deficient in that it does not specifically teach the use of fragmentation prior to subjecting it to mass spectrometry.

However, Loo teaches the following limitations that Pitner et al lacks:

For **claims 47-48**, Loo teaches the use of mass spectroscopy for the "identification of novel protein-ligand interactions" including "antibody-antigen" conjugates (see Loo, entire document, especially page 14, section VI, paragraph 2, see also page 2, paragraph 1; see also abstract; see especially Table 1 showing many examples of protein-ligand interactions being studied by mass spectroscopy).

For **claim 49**, Loo et al teaches fragmentation via tandem mass spectrometry (see Loo, page 4, column 1, paragraph 3).

It would have been obvious to one skilled in the art at the time the invention was made to "identify" antibody/antigen interactions using the method steps as taught by Pitner et al in conjunction with the mass spectrometer techniques for the "identification of novel protein-ligand interactions" as taught by Loo because Loo explicitly states that the mass spectrometry can be applied to a broad range of protein-ligand interactions including "antibody-antigen" complexes (see Loo, page 2, paragraph 1), which would

encompass the "antibody-antigen" complexes of Pitner et al. Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Loo with the antibody-antigen conjugates as taught by Pitner et al because Loo explicitly states that mass spectroscopy offers many advantages including speed, sensitivity, stoichiometry and mass accuracy (see Loo, abstract, see also page 4, column 1) for analyzing the protein/ligand interactions and their binding affinities.

Response

12. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues **[1]** that there is no motivation to combine the references "since antibodies are raised against antigens, the antigen of any particular antibody is, by definition, known. Accordingly, one ... would not be motivated to search for any method for identifying the antigens present in the antigen-antibody complexes" (see Paper No. 12, page 13), **[2]** Loo deals only with "non-covalent complexes" not the "covalent" complexes of Pitner et al (see Paper No. 12, page 14) and **[3]** the combined references do not teach all the limitations because Pitner et al is deficient.

This is not found persuasive for the following reasons:

The Examiner contends **[1]** that a person of skill would be motivated to identify which "known" antigens bind to ascertain the "binding affinity" not the "chemical identity" as purported by Applicants (see Paper No. 12, page 13). Please note that "there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention", see MPEP § 2144").

The Examiner further contends **[2]** that Loo does teach that both "covalent" and "non-covalent" interactions can be analyzed with a mass spectrometer and explicitly states that the mass spectrometry can be applied to a broad range of protein-ligand interactions including "antibody-antigen" complexes (see Loo, page 2, paragraph 1), which would encompass the "antibody-antigen" complexes of Pitner et al.

For example, Loo teaches both "covalent" and "non-covalent" interactions and explicitly states that it can be used for antibody-antigen complexes like the ones used in Pitner et al (see Loo, page 2, paragraph 1). For example, Loo et al discloses a peak at 1972 for the "non-covalent" complex of (SRC with Ac-QpYEEIP-NH2)$^{7+}$ and also another peak at 1614 for the uncomplexed SRC (SRC)$^{8+}$ (see Loo et al, page 11, figure 4). The 1972 peak clearly demonstrates that mass spectroscopy can be used to identify "non-covalent" complexes because the 1972 peak represents the molecular weight of Src complexed non-covalently to Ac-QpYEEIP-NH_2. However, the spectrum further shows a peak at 1614 for the un-complexed Src, which contains many "covalent" bonds (e.g., Src is a protein which has many "covalent" bonds such as the covalent bonds that connect the peptide backbone or the amino acid side chains). Consequently, it would be immediately obvious to a person of skill in the art that "covalent" bonds do NOT interfere with experiment (i.e., the fact that Src has "covalent" bonds does not

render it undetectable in a mass spectrometer). Therefore, Loo does not teach a "completely different problem" than Pitner et al as purported by Applicants because the physical distinction between "covalent" and "non-covalent" interactions as applied to mass spectroscopy is of no practical consequence (as shown above). A person of skill in the art would have been motivated to combine Pitner et al with Loo et al because Loo et al explicitly states that mass spectrometry can be used for antibody-antigen complexes like the ones disclosed by Pitner et al (see Loo et al, page 6294, paragraph 1) whether they are of a "covalent" nature or not.

Furthermore, as stated above a person of skill in the art would be motivated to use mass spectroscopy precisely because it does detect BOTH "covalent" and "non-covalent" bonds and, as a result, could help distinguish between modified antibodies that are binding to their antigens via the desired "covalent" bonds versus any unwanted "non-covalent" interactions that might occur through conformational changes to the antibody upon modification (e.g., with a sulfhydryl group).

Finally, the Examiner's position is **[3]** that Pitner et al is not deficient for the reasons stated above (see response to 35 U.S.C. § 102) and thus the combined references do teach all of the claimed limitations.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

13. Claims 40-41, 44-48 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**) and Ganem et

al (Ganem, B.; Li, Y. T.; Henion, J. D. "Detection of noncovalent receptor-ligand complexes by mass spectrometry" *Journal of the American Chemical Society* **1991**, 113(16), 6294-6).

For **claims 40-41 and 44-46**, Pitner et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 40-41 and 44-46 and, consequently, also renders obvious claims 40-41 and 44-46.

The prior art teachings of Pitner et al differ from the claimed invention as follows:

For **claims 47-48**, Pitner et al is deficient in that it does not specifically teach the use of "mass spectrometry" for the identifying step. Pitner et al used UV/Vis for detection.

However, Ganem et al teaches the following limitations that Pitner et al lacks:

For **claim 47-48**, Ganem et al (see entire document) teaches the use of mass spectroscopy for "identifying enzyme-substrate, receptor-ligand ... complexes" (see Ganem et al, page 6294, paragraph 1; see also, page 6295, second column, last paragraph). Furthermore, Ganem et al teaches that the ligand can be "identified" using mass spectrometry without purification (see Ganem et al, page 6296, "This result indicates that noncovalently bound species can be detected directly in a complex mixture without chromatographic separation"; see also figure 3, peak 1803.1 showing FKBP/FK506 complex).

It would have been obvious to one skilled in the art at the time the invention was made to "screen a library of small organic compounds" as taught by Pitner et al in

conjunction with the mass spectrometer techniques as taught by Ganem et al because Ganem et al explicitly states that the mass spectrometry "can be applied to problems of biological interest [including] ... proteins" and that the methods are good for "detecting and identifying enzyme-substrate, receptor-ligand [complexes]", (see Ganem et al, page 6294, paragraph 1) (see also page 6296 wherein Ganem specifically refers to "antibody-antigen" complexes as well), which would encompass the "antibody-antigen" complexes of Pitner et al. Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Ganem et al with the ligand-receptors as taught by the teachings of Pitner et al because Ganem et al explicitly states that the "ion-spray MS can be performed in water without cosolvent, which is ideal for most biological systems. Multiple charging produces a family of molecular ions and dramatically reduces the mass-to-charge ratio so that even quadrupole mass spectrometers having a typical range of 1000-2000 daltons (DA) can determine high MW species with unit mass resolution" (see Ganem et al, page 6294, second paragraph) (see also Ganem et al, page 6296, last paragraph).

Finally, the Examiner's position is **[3]** that Pitner et al is not deficient for the reasons stated above (see response to 35 U.S.C. § 102) and thus the combined references do teach all of the claimed limitations.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Response

14. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues **[1]** that there is no motivation to combine the references "since antibodies are raised against antigens, the antigen of any particular antibody is, by definition, known. Accordingly, one ... would not be motivated to search for any method for identifying the antigens present in the antigen-antibody complexes" (see Paper No. 12, page 15, paragraph 1), **[2]** Loo deals only with "non-covalent complexes" not the "covalent" complexes of Pitner et al (see Paper No. 12, page 14) and **[3]** the combined references do not teach all the limitations because Pitner et al is deficient.

This is not found persuasive for the following reasons:

The Examiner contends **[1]** that a person of skill would be motivated to identify which "known" antigens bind to ascertain the "binding affinity" not the "chemical identity" as purported by Applicants (see Paper No. 12, page 15, paragraph 1). Please note that "there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention", see MPEP § 2144").

The Examiner also contends **[2]** that Ganem et al does NOT teach exclusively "non-covalent" interactions as alluded to by Applicants and is NOT addressing a "completely different problem" (see Paper No. 10, page 11, paragraph 5). Ganem teaches both "covalent" and "non-

covalent" interactions and explicitly states that it can be used for antibody-antigen complexes like the ones used in Pitner et al (see Ganem et al, page 6294, paragraph 1). For example, Ganem et al discloses a peak at 1803.1 for the "non-covalent" complex of (FKBP + FK506 + 7H)$^{7+}$ and also another peak at 1969.8 for the un-complexed FKBP (FKBP + 6H)$^{6+}$ (see Ganem et al, page 6295, figure 4). The 1803.1 peak clearly demonstrates that mass spectroscopy can be used to identify "non-covalent" complexes because the 1803.1 peak represents the molecular weight of FKBP complexed non-covalently to FK506. However, the spectrum further shows a peak at 1969.8 for the un-complexed FKBP, which contains many "covalent" bonds (e.g., FKBP is a small hydrophilic protein which has many "covalent" bonds such as the covalent bonds that connect the peptide backbone or the amino acid side chains). Consequently, it would be immediately obvious to a person of skill in the art that "covalent" bonds do NOT interfere with experiment (i.e., the fact that FKBP has "covalent" bonds does not render it undetectable in a mass spectrometer). In fact, if the mass spectrometer could not detect "covalent" bonds as purported by Applicants then the mass spectrometer would not provide the signals shown in figure 4 of Ganem et al because both the FKBP and the FK506 have "covalent" bonds. Therefore, Ganem et al do not teach a "completely different problem" than Pitner et al as purported by Applicants because the physical distinction between "covalent" and "non-covalent" interactions as applied to mass spectroscopy is of no practical consequence. A person of skill in the art would have been motivated to combine Pitner et al with Ganem et al because Ganem et al explicitly states that mass spectrometry can be used for antibody-antigen complexes like the ones disclosed by Pitner et al (see Ganem et al, page 6294, paragraph 1) whether they are of a "covalent" nature or not.

Furthermore, as stated above a person of skill in the art would be motivated to use mass spectroscopy precisely because it does detect BOTH "covalent" and "non-covalent" bonds and, as a result, could help distinguish between modified antibodies that are binding to their antigens via the desired "covalent" bonds versus any unwanted "non-covalent" interactions that might occur through conformational changes to the antibody upon modification (e.g., with a sulfhydryl group).

Finally, the Examiner's position is **[3]** that Pitner et al is not deficient for the reasons stated above (see response to 35 U.S.C. § 102) and thus the combined references do teach all of the claimed limitations.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

15. Claims 40-41, 44-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**) and Przybylski et al (Przybylski, M.; Glocker, M. O. "Electrospray Mass Spectrometry of Biomacromolecular Complexes with Noncovalent Interactions-New Analytical Perspecties for Supramolecular Chemistry and Molecular Recognition Processes" Angew. Chem. Int. Ed. Engl. **1996**, 35, 806-826) and Wunsch et al (Wunsch, E.; Spangenberg, R., in Peptides, 1969, E. Schoffone, Ed., North Holland, Amsterdam, P. 1971. Please note the original reference will be provided when it becomes available; an excerpt from Greene, T. W. et al is provided which references the Wunsch article i.e., Greene, T. W.; Wuts, P. G. M. in Protective Groups in Organic Synthesis, 1999, John

Wiley & Sons, Inc., New York, page 487) (This reference is provided solely to show the state of the art with regard to disulfide bond cleavage).

For **claims 40-41 and 44-46**, Pitner et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 40-41 and 44-46 and, consequently, also renders obvious claims 40-41 and 44-46.

The prior art teachings of Pitner et al differ from the claimed invention as follows:

For **claims 47-48**, Pitner et al is deficient in that it does not specifically teach the use of "mass spectrometry" for the identifying step. Pitner et al used UV/Vis for detection.

For **claim 49**, Pitner et al is deficient in that it does not specifically teach the use of fragmentation prior to subjecting it to mass spectrometry.

For **claims 50-52**, Pitner et al is deficient in that it does not specifically teach the use of liberating or releasing the small organic compound from the complex prior to subjecting it to mass spectrometry.

However, Przybylski et al teaches the following limitations that Pitner et al lacks:

For **claim 47-48**, Przybylski et al (see entire document) teaches the use of mass spectroscopy for "receptor-ligand interactions" including "antibody-antigen" interactions (see Przybylski et al, page 823, last paragraph; see also page 808, column 1, paragraph 1; see also abstract; see also page 812, section 2.3, paragraph 1). Furthermore, Przybylski et al teaches that the ligand can be "identified" using mass spectrometry without

purification (see Przybylski et al, page 808, column 2, paragraph 2, "ESI-MS is applicable to relatively impure samples").

For **claim 49**, Przybylski et al teaches the use of fragmentation both by enzymatic techniques (i.e., fractionation by enzyme cleavage before detection) and by the use of mass spectrometry techniques e.g., tandem-ESI-MS upon collision induced dissociation (see Przybylski et al, figure 9; see also page 817, column 1, paragraph 2).

For **claims 50-52**, Przybylski et al teaches the use of DTT (see Figure 9, bottom spectrum). Furthermore, applicant's specification does not teach the criticality of using one particular agent and, as a result, any reducing agent would be immediately envisaged for this application including sodium borohydride and any other common reducing agents known in the art see Wunsch et al (Wunsch, E.; Spangenberg, R., in Peptides, 1969, E. Schoffone, Ed., North Holland, Amsterdam, P. 1971 (This reference is provided solely to show the state of the art with regard to disulfide bond cleavage showing cleavage of s-*t*-butyl disulfide with sodium borohydride).

It would have been obvious to one skilled in the art at the time the invention was made to "screen a library of small organic compounds" as taught by Pitner et al in conjunction with the mass spectrometer techniques as taught by Przybylski et al because Przybylski et al explicitly states that the mass spectrometry can be applied to "antibody-antigen" complexes (see Przybylski et al, page), which would encompass the "antibody-antigen" complexes of Pitner et al and, consequently, the Przybylski et al reference would point one of ordinary skill to the Pitner et al reference. Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by

Przybylski et al with the ligand-receptors as taught by the teachings of Pitner et al because Przybylski et al explicitly states many advantage of mass spectroscopy for studying protein-ligand interactions including [a] "breakthrough" to macromolecules larger than 100 kDa, [b] high resolution, [c] usefulness in determining protein-ligand stoichiometries, [d] determinations of equilibrium constants, and [e] the fact that ESI-MS can be readily carried out with aqueous solutions at nearly physiological solution condition, thus enabling comparison with other methods of structure determination and NMR spectrscopy (see Przybylski et al, abstract; see also page 815, column 2, paragraph 1; see also page 816, column 2, paragraph 1; see also page 808, column 2, paragraph 1). A person of skill in the art would have reasonably expected to be successful because Przybylesk et al provides many examples of successful application of ESI-MS to protein-ligand conjugates including combinatorial screening (see entire document, especially page 823, last paragraph).

Response

16. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues **[1]** that there is no motivation to combine the reference because the "antigens" are already known, **[2]** Pryzybylski et al concerns only "non-covalent" interactions

and, as a result, Pitner et al would not turn to Pryzybylski et al and **[3]** that the combined references do not teach all the limitations because Pitner et al is deficient (see Paper No. 12, page16).

This is not found persuasive for the following reasons:

The Examiner contends **[1]** that a person of skill would be motivated to identify which "known" antigens bind to ascertain the "binding affinity" not the "chemical identity" as purported by Applicants (see Paper No. 12, page 15, paragraph 1). Please note that "there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention", see MPEP § 2144").

The Examiner contends **[2]** that as stated above for Ganem et al and Loo et al (which is incorporated here by reference) a person of skill in the art would readily understand that mass spectroscopy is broadly applicable to a broad range of compounds that would include both "covalent" and "non-covalent" compounds and/or complexes. Thus, the distinction that Applicants rely on here (i.e., covalent v. non-covalent) is simply without merit.

Finally, the Examiner contends **[3]** that that Pitner et al is not deficient for the reasons stated above (see response to 35 U.S.C. § 102) and thus the combined references do teach all of the claimed limitations.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

17. Claims 40-41, 44-52, 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janda et al (Janda, K. D.; Lo, C. –H. L.; Li, T.; Barbas, C. F.; Wirsching, P.; Lerner, R. A.

"Direct selection for a catalytic mechanism from combinatorial antibody libraries" *PNAS* **March 1994**, *91*, 2532-2536) and Przybylski et al (Przybylski, M.; Glocker, M. O. "Electrospray Mass Spectrometry of Biomacromolecular Complexes with Noncovalent Interactions-New Analytical Perspecties for Supramolecular Chemistry and Molecular Recognition Processes" Angew. Chem. Int. Ed. Engl. **1996**, 35, 806-826) and Wunsch et al (Wunsch, E.; Spangenberg, R., in Peptides, 1969, E. Schoffone, Ed., North Holland, Amsterdam, P. 1971. Please note the original reference will be provided when it becomes available; an excerpt from Greene, T. W. et al is provided which references the Wunsch article i.e., Greene, T. W.; Wuts, P. G. M. in Protective Groups in Organic Synthesis, 1999, John Wiley & Sons, Inc., New York, page 487) (This reference is provided solely to show the state of the art with regard to disulfide bond cleavage).

For **claims 40-41 and 44-46**, Janda et al teaches all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 40-41, 44-46, 56 and, consequently, also renders obvious claims 40-41, 44-46 and 56.

The prior art teachings of Janda et al differ from the claimed invention as follows:

For **claims 47-48**, Janda et al is deficient in that it does not specifically teach the use of "mass spectrometry" for the identifying step. Janda et al used UV/Vis for detection.

For **claim 49**, Janda et al is deficient in that it does not specifically teach the use of fragmentation prior to subjecting it to mass spectrometry.

For **claims 50-52**, Janda et al is deficient in that it does not specifically teach the use of liberating or releasing the small organic compound from the complex prior to subjecting it to mass spectrometry. Janda et al only teaches the use of liberating the small organic molecule without using mass spectrometry (see Figure 2, application of DTT; see also page 2534, column 1, paragraph 1 showing use of Elman's reagent).

However, Przybylski et al teaches the following limitations that Janda et al lacks:

For **claim 47-48**, Przybylski et al (see entire document) teaches the use of mass spectroscopy for "receptor-ligand interactions" including "antibody-antigen" interactions (see Przybylski et al, page 823, last paragraph; see also page 808, column 1, paragraph 1; see also abstract; see also page 812, section 2.3, paragraph 1). Furthermore, Przybylski et al teaches that the ligand can be "identified" using mass spectrometry with or without purification (see Przybylski et al, page 808, column 2, paragraph 2, "ESI-MS is applicable to relatively impure samples and multicomponent mixtures and is compatible with microanalytical separation techniques").

For **claim 49**, Przybylski et al teaches the use of fragmentation both by enzymatic techniques (i.e., fractionation by enzyme cleavage before detection) and by the use of mass spectrometry techniques e.g., tandem-ESI-MS upon collision induced dissociation (see Przybylski et al, figure 9; see also page 817, column 1, paragraph 2).

For **claims 50-52**, Przybylski et al teaches the use of DTT (see Figure 9, bottom spectrum). Furthermore, applicant's specification does not teach the criticality of using one particular agent and, as a result, any reducing agent would be immediately envisaged for this application including sodium borohydride and any other common reducing agents

known in the art Wunsch et al (Wunsch, E.; Spangenberg, R., in Peptides, 1969, E. Schoffone, Ed., North Holland, Amsterdam, P. 1971. Please note the original reference will be provided when it becomes available; an excerpt from Greene, T. W. et al is provided which references the Wunsch article i.e., Greene, T. W.; Wuts, P. G. M. in Protective Groups in Organic Synthesis, 1999, John Wiley & Sons, Inc., New York, page 487) (This reference is provided solely to show the state of the art with regard to disulfide bond cleavage showing cleavage of s-*t*-butyl disulfide with sodium borohydride).

It would have been obvious to one skilled in the art at the time the invention was made to "screen a library" as taught by Janda et al in conjunction with the mass spectrometer techniques as taught by Przybylski et al because Przybylski et al explicitly states that the mass spectrometry can be applied to "antibody-antigen" complexes (see Przybylski et al, page), which would encompass the "antibody-antigen" complexes of Janda et al and, consequently, the Przybylski et al reference would point one of ordinary skill to the Janda et al reference. Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Przybylski et al with the ligand-receptors as taught by the teachings of Janda et al because Przybylski et al explicitly states many advantage of mass spectroscopy for studying protein-ligand interactions including [a] "breakthrough" to macromolecules larger than 100 kDa, [b] high resolution, [c] usefulness in determining protein-ligand stoichiometries, [d] determinations of equilibrium constants, and [e] the fact that ESI-MS can be readily carried out with aqueous solutions at nearly physiological solution condition, thus enabling comparison with other methods of structure determination and NMR

spectrscopy (see Przybylski et al, abstract; see also page 815, column 2, paragraph 1; see also page 816, column 2, paragraph 1; see also page 808, column 2, paragraph 1). A person of skill in the art would have reasonably expected to be successful because Przybylesk et al provides many examples of successful application of ESI-MS to protein-ligand conjugates including combinatorial screening (see entire document, especially page 823, last paragraph).

Response

18. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues **[1]** that the combined references do not teach all the limitations because Janda et al is deficient (see Paper No. 12, page17) and **[2]** the secondary references (discussed in the previous rejections) do not supply the teachings missing from Janda

This is not found persuasive for the following reasons:

The Examiner contends **[1]** that that Janda et al is not deficient for the reasons stated above (see response to 35 U.S.C. § 102) and thus the combined references do teach all of the claimed limitations.

The Examiner contends **[2]** that Applicants do no explicitly state what deficiencies are in the secondary references here and, as a result, those deficiencies must have already been addressed in the previous responses (which are incorporated herein by record).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

19. Claims 40-41 and 44-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**) and Przybylski et al (Przybylski, M.; Glocker, M. O. "Electrospray Mass Spectrometry of Biomacromolecular Complexes with Noncovalent Interactions-New Analytical Perspecties for Supramolecular Chemistry and Molecular Recognition Processes" Angew. Chem. Int. Ed. Engl. **1996**, 35, 806-826) and Crooke et al (US Patent No. 6,428,956) (Filing Date is **May 12, 1998**).

For **claims 40-41 and 44-52**, the combined teachings of Pitner et al and Przybylski et al teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 40-41 and 44-52 and 56.

The combined prior art teachings of Pitner et al and Przybylski et al differ from the claimed invention as follows:

For **claim 53**, the combined teachings of Pitner et al Pryzybylski et al are deficient in that it does not teach the use of labeled probes.

However, Crooke et al teaches the following limitations that the combined teachings of Pitner et al and Przybylski et al lack:

For **claim 53**, Crooke et al (see entire document) teaches the use mass tags in combinatorial screening techniques (see Crooke et al, column 7, paragraph 2), which

anticipates the "labled probes" because the masked tag acts to label the compounds via a mass label.

It would have been obvious to one skilled in the art at the time the invention was made to "screen a library" as taught by Pitner et al in conjunction with the mass spectrometer techniques as taught by Przybylski et al and in further conjunction with the "mass tags" (i.e., labeled probes) as taught by Crooke et al because Crooke et al explicitly states that the mass tags can be used for receptor-ligand complexes (see Crooke et al, abstract), which would encompass the "antibody-antigen" complexes (Crooke et al also sites various antibody-antigen papers as examples). One would have been motivated to use the "mass labels" of Crooke et al because according to Crooke they are useful in situations where "mass redundancy is a concern, especially if two or more targets are of similar ... mass" (see Crooke et al, column 7, second paragraph; see also claims e.g., 1, 4, 6, 7, 10, 11; see also column 23, line 29).

Response

20. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues that neither Pitner et al nor Przybylski et al teach all elements of the invention as claimed in claims 40-41 and 44-5 (see Paper No. 12, page 18, paragraph 2) and thus combination with Crooke et al is also inadequate.

This is not found persuasive for the following reasons:

The Examiner contends that as discussed above Pitner et al and Przybylski et al do teach all the limitations in claims 40-41 and 44-45 (see above rejections which are incorporated herein by record) and thus the combination with Crooke et al is proper.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

21. Claims 40-41, 44-53 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Janda et al (Janda, K. D.; Lo, C. –H. L.; Li, T.; Barbas, C. F.; Wirsching, P.; Lerner, R. A. "Direct selection for a catalytice mechanism from combinatorial antibody libraries" *PNAS* **March 1994**, *91*, 2532-2536) and Przybylski et al (Przybylski, M.; Glocker, M. O. "Electrospray Mass Spectrometry of Biomacromolecular Complexes with Noncovalent Interactions-New Analytical Perspecties for Supramolecular Chemistry and Molecular Recognition Processes" Angew. Chem. Int. Ed. Engl. **1996**, 35, 806-826) and Crooke et al (US Patent No. 6,428,956) (Filing Date is **May 12, 1998**).

For **claims 40-41, 44-52 and 56**, the combined teachings of Janda et al and Przybylski et al teach all the limitations stated in the 35 U.S.C. 103(a) rejection above

(incorporated in its entirety herein by reference), which renders obvious claims 40-41 and 44-52 and 56.

The combined prior art teachings of Janda et al and Przybylski et al differ from the claimed invention as follows:

For **claim 53**, the combined teachings of Janda et al Pryzybylski et al are deficient in that it does not teach the use of labeled probes.

However, Crooke et al teaches the following limitations that the combined teachings of Janda et al and Przybylski et al lack:

For **claim 53**, Crooke et al (see entire document) teaches the use mass tags in combinatorial screening techniques (see Crooke et al, column 7, paragraph 2), which anticipates the "labled probes" because the masked tag acts to label the compounds via a mass label.

It would have been obvious to one skilled in the art at the time the invention was made to "screen a library" as taught by Janda et al in conjunction with the mass spectrometer techniques as taught by Przybylski et al and in further conjunction with the "mass tags" (i.e., labeled probes) as taught by Crooke et al because Crooke et al explicitly states that the mass tags can be used for receptor-ligand complexes (see Crooke et al, abstract), which would encompass the "antibody-antigen" complexes (Crooke et al also sites various antibody-antigen papers as examples). One would have been motivated to use the "mass labels" of Crooke et al because according to Crooke they are useful in situations where "mass redundancy is a concern, especially if two or more targets are of

similar ... mass" (see Crooke et al, column 7, second paragraph; see also claims e.g., 1, 4, 6, 7, 10, 11; see also column 23, line 29).

Response

22. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicant argues **[1]** that the previous combination of Janda et al and Przybylski et al is improper (see Paper No. 12, page 18, paragraph 2) and thus combination with Crooke et al is also improper and **[2]** Crooke et al does not remedy the deficiencies of Janda et al and Przybylski et al.

This is not found persuasive for the following reasons:

The Examiner contends that **[1]** as discussed above the combination of Janda et al with Przybylski et al is proper (see above rejections which are incorporated herein by record) and thus the combination with Crooke et al is also proper.

The Examiner contends that **[2]** Crooke et al does remedy the deficiencies of Janda et al and Przybylski et al for the reasons of records (see original rejection).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Double Patenting

23. Claims 40-41, 44-53, 56 and 63 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent Application Publication 2002/0022233 A1 (see especially claims 12-31 of '233). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the referenced patent are drawn essentially to same method of screening a library and, as a result, the inventions overlap in scope. For example, both references recite [a] method steps for screening a library of small organic compounds (compare claim 14 of '233 to claim 40 of the present application), [b] with a target protein-ligand conjugate formed by the covalent bonding of a biological target molecule comprising a first reactive functionality with a compound that comprises a second reactive functionality and a chemically reactive group (compare claims 13, 14 (b) and 19 of '233 to claim 40 of the present application), [c] wherein the second reactive functionality of he compound reacts with the first reactive functionality of the biological target molecule to form a first covalent bond such that the protein-ligand conjugate contains a free chemically reactive group under conditions wherein at least one member of the library forms a second covalent (compare claim 14 (c) and 19 of '233 to claim 40 of the present application), and [d] identifying a small organic compound that binds covalently to the chemically reactive group thereby forming a covalent complex (compare claims 14 (d) of '233 to claim 40 (b) of the present application). Accordingly it is deemed that the inventions claimed herein and that of the patent are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

24. Claims 40-41, 44-53, 56 and 63 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-39 of U.S. Patent Application Publication 2002/0081621 A1 (see especially claims 13-31 of '621). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the referenced patent are drawn essentially to same method of screening a library and, as a result, the inventions overlap in scope. For example, both references recite [a] method steps for screening a library of small organic compounds (compare claim 14 of '621 to claim 40 of the present application), [b] with a target protein-ligand conjugate formed by the covalent bonding of a biological target molecule comprising a first reactive functionality with a compound that comprises a second reactive functionality and a chemically reactive group (compare claims 13, 14 (b) and 19 of '621 to claim 40 of the present application), [c] wherein the second reactive functionality of he compound reacts with the first reactive functionality of the biological target molecule to form a first covalent bond such that the protein-ligand conjugate contains a free chemically reactive group under conditions wherein at least one member of the library forms a second covalent bond (compare claim 14 (c) and 19 of '621 to claim 40 of the present application), and [d] identifying a small organic compound that binds covalently to the chemically reactive group thereby forming a covalent complex (compare claims 14 (d) of '621 to claim 40 (b) of the present application). Accordingly it is deemed that the inventions claimed herein and that of the patent are obvious variants of each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response

25. Applicants' arguments directed to the above double patenting rejections were fully considered but were not deemed persuasive for the following reasons.

Applicants argue that the double patenting rejection should be "repeated in one or both of the pending parallel applications" instead of the present application (see Paper No. 12, page 19, paragraph 3).

This is not found persuasive for the following reasons:

The Examiners position is that Applicants must file a terminal disclaimer in each application including the present application (see MPEP § 804.02, "If an appropriate double patenting rejection of the nonstatutory type is made in two or more pending applications, an appropriate terminal disclaimer must be filed in each application"; see also MPEP § 1490, Two or More Copending Applications section, "If two (or more) pending applications are filed in each of which a rejection of one claimed invention over the other on the ground of obviousness-type double patenting is proper, the rejection will be made in each application. An appropriate terminal disclaimer must be filed in each application. This is because a terminal disclaimer filed to obviate a double patenting rejection is effective only with respect to the application identified in the disclaimer. Moreover, the filing of an appropriate terminal disclaimer in each application will prevent a potential improper timewise extension of patent rights in the last application to be issued").

Accordingly, the double patenting rejection cited above is hereby maintained.

New Rejections

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

26. Claims 40-41, 44-53, 56 and 63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. For **claim 40**, the phrase "ligand in the protein-ligand conjugate" is vague and indefinite. For example, it is not clear whether the "ligand" that is being referred to in the newly amended claim is the "compound" that "comprises (1) a second reactive functionality and (2) a chemically reactive group" and if it is then the Examiner contends that Applicants should use a consistent notation throughout the claims to describe this "compound or ligand" to avoid confusion. Is the "ligand" = the "compound"? Applicants are requested to clarify. Therefore, claim 40 and all dependent claims are rejected under 35 U.S.C. 112, second paragraph.

B. **Claim 40** recites the limitation "the ligand" in the 7th line. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 40 and all dependent claims are rejected under 35 USC 112, second paragraph.

C. **Claim 48** recites the limitation "the target protein-ligand conjugate" in the last line. There is insufficient antecedent basis for this limitation in the claim. Therefore, claim 48 and all dependent claims are rejected under 35 USC 112, second paragraph.

Claims Rejections - 35 U.S.C. 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

27. Claims 40-41, 44-53, 56 and 63 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed had possession of the claimed invention. This is a new matter rejection.

A. In newly amended claim 40, to the extent that the phrase "target molecule" extends to go beyond the definition of a "biological target molecule", the increased breadth of possible modification constitutes new matter (i.e., the breadth of the target molecule has now been increased from only biological targets to non-biological targets), since there is no specification support or original claim support for such scope; nor has applicant provided any indication where such support exists. If applicant believes this rejection is in error, applicant must disclose where in the specification support for this amendment can be found in accordance with MPEP 714.02. Therefore, claim 40 and all

claims from which 40 depends represent new matter i.e., claims 40-41, 44-53, 56 and 63.

Claim Rejections - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

30. Claims 40-41, 44-52 and 63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pitner et al (U.S. Pat. No. 5,367,058) (Date of Patent is **November 22, 1994**) and Przybylski et al (Przybylski, M.; Glocker, M. O. "Electrospray Mass Spectrometry of Biomacromolecular Complexes with Noncovalent Interactions-New Analytical Perspectives for Supramolecular Chemistry and Molecular Recognition Processes" Angew. Chem. Int. Ed. Engl.

1996, 35, 806-826) and Wunsch et al (Wunsch, E.; Spangenberg, R., in Peptides, 1969, E. Schoffone, Ed., North Holland, Amsterdam, P. 1971. Please note the original reference will be provided when it becomes available; an excerpt from Greene, T. W. et al is provided which references the Wunsch article i.e., Greene, T. W.; Wuts, P. G. M. in Protective Groups in Organic Synthesis, 1999, John Wiley & Sons, Inc., New York, page 487) (This reference is provided solely to show the state of the art with regard to disulfide bond cleavage) and Tam (U.S. Patent No. 6,310,180) (Filing Date is **June 19, 1995**).

For **claims 40-41 and 44-52**, the combined teachings of Pitner et al, Przybylski et al, Wunsch et al, Greene et al [referred to herein as just Pitner et al] teach all the limitations stated in the 35 U.S.C. 103(a) rejection above (incorporated in its entirety herein by reference), which renders obvious claims 40-41 and 44-52.

The prior art teachings of Pitner et al differ from the claimed invention as follows:

For **claims 63**, Pitner et al is deficient in that it does not specifically teach the use of tris-2-carboxyethyl)-phosphine (TECP).

However, Tam et al teaches the following limitations that Pitner et al lacks:

For **claims 63**, Tam et al teaches the use of TECP (see Tam, column 41, line 7). Applicant's specification does not teach the criticality of using one particular agent and, as a result, "any" reducing agent would be immediately envisaged including the TECP agent disclosed by Tam et al.

It would have been obvious to one skilled in the art at the time the invention was made to use TECP because Tam teaches that it was a common reducing agent used with

proteins. Furthermore, one of ordinary skill in the art would have been motivated to use TECP because Tam shows that it can be used with antibodies as disclosed by Pitner et al.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D. Epperson, Ph.D. whose telephone number is (703) 308-2423. The examiner can normally be reached on Monday-Thursday from 9:30 to 7:00 and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Jon D. Epperson, Ph.D.
June 14, 2003

BENNETT CELSA
PRIMARY EXAMINER